Toxicology Excellence for Risk Assessment

TERA

a nonprofit corporation dedicated to the best use of toxicity data for risk values

October 31, 2000

Mr. Harry Browne
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Dear Mr. Browne:

Thank you for contacting *TERA* regarding the Human Health Risk Assessment for the Hurley Soils Investigation Unit. As you know, *TERA* allocates 10 hours of pro bono work to each state each year to assist in providing risk assessment information. Your request is being handled through this mechanism.

TERA had previously replied to your initial inquiries from George Schuman of the NMED by email on July 21, 2000. The reply prompted more questions from your group as well as additional questions from Mr. Schuman. Below, please find *TERA*'s answers to those questions.

<u>Does the HHRA reflect the current state of science on copper toxicity?</u> The science on chronic toxicity of copper for both inhalation and oral exposure routes is not very robust. The majority of research with copper intake has centered on copper deficiency, adequacy and inborn errors of metabolism. Very little research has been performed to systematically look at the effects of excess copper in humans or other mammals. The best information available on excess copper in humans come from anecdotal reports of the acute effects of copper following drinking water ingestion. The HHRA captures this information and is adequately presented in the report. Unfortunately, the work that I have been involved with has only recently been submitted for publication and cannot be cited at this time. However, a preliminary description of this study can be found as an abstract[1]. There was a recent publication from Santiago, Chile[2] on copper in drinking water published in the last year that was not cited in the HHRA, although it may not have been available when this report was prepared.

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[1] Poirier, KA, M Araya, LM Klevay, JJ Strain, FH Nielsen, P Robson, MC McGoldrick and SR Baker. Determination of a human acute no observed adverse effect level (NOAEL) for copper. The Toxicologist 54:73, 2000.

[2] Pizarro F, M Olivares, R Uauy, P Contreras, A Rebelo, and G Gidi. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspectives 107 (2):117-121, 1999.

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In the only published controlled human study reported to date, Pizarro et al. determined the acute gastrointestinal effects in 60 adult Chilean females who were each given 0, 1, 3, or 5 mg Cu/L in a public (tap) drinking water source. This was the sole drinking water source for these individuals for a 2-week period. Mild gastrointestinal disturbances (nausea, abdominal pain, vomiting and diarrhea) were recorded at least once in 35% of the subjects. Nausea, abdominal pain and vomiting were significantly related to copper concentrations with a recorded incidence of 5, 2, 17 and 15% in the individuals consuming 0, 1, 3, or 5 mg Cu/L, respectively, suggesting that copper concentrations greater than 3 mg Cu/L can be associated with these gastrointestinal symptoms.

The data reported by Pizarro et al., is consistent with the data that was collected in the international study that *TERA* has coordinated for the International Copper Association (ICA). These data examined in combination suggests that consumption of water greater than 4 mg Cu/L will significantly increase the chance of experiencing mild gastrointestinal symptoms, particularly nausea. Differences in experimental protocol (source of water, frequency of consumption, subject size, experimental design) may account for the slight difference in the apparent respective acute NOAELs for copper between these two studies.

More specifically, the ICA sponsored a prospective, double blind controlled a target of 60 adults, 30 of each sex and 18-60 years of age. Subjects were recruited at three different international sites (Grand Forks, ND, USA; Coleraine, Northern Ireland; Santiago, Chile) and given solutions containing 0, 2, 4, 6, and 8 mg Cu/L (as copper sulfate). Each subject was given a blind, randomly selected dose in a bolus of 200 ml (final total copper dose was equivalent to 0, 0.4, 0.8, 1.2, and 1.6 mg) once weekly over a consecutive 5 week period. All subjects completed questionnaires at 0 time, 15 minutes, 1 hour and 24 hours that screened for positive GI effects (nausea, vomiting, abdominal pain, and diarrhea). Nausea was the most frequently reported effect and was reported within the first 15 minutes of ingestion. All other GI effects were reported within 1 hour. For the combined tri-site population (n = 179), 8, 9, 14, 25 and 44 subjects responded positively to one or more GI symptoms at 0, 2, 4, 6 and 8 mg Cu/L, respectively. Analysis of the data demonstrated a clear dose response to the combined positive GI effects and to nausea alone. Statistically significant greater reporting of effects occurred at 6 and 8 mg Cu/L. Therefore, an acute NOAEL and Lowest-Observed-Adverse-Effect Level (LOAEL) of 4 and 6 mg Cu/L, respectively were determined in drinking water for a combined international human population.

<u>Does the HHRA adequately consider both acute and chronic effects of copper?</u> As stated above, very little is known about copper's toxicity for a chronic exposure period. The acute data, even though anecdotal, unreliable and not reproducible, is the best available data that we have to estimate a risk assessment for copper. The GI effects are primarily reported. Little is known of copper's effect on other organ systems except in known genetically susceptible subpopulations.

<u>Is Gradient's recommended RfD appropriate?</u> No. The HHRA used the Wyllie anecdotal data to estimate the RfD. These data are not well characterized for dose response. The dose used is an average estimate and does not accurately represent copper inducing the GI effects. The LOAEL is a best guess estimate. In light of the emerging controlled human exposure studies, I would recommend using the Pizarro et al. study cited above to develop a RfD. There is precedent within the US EPA for developing RfDs using acute exposure periods, *e.g.* Nitrate and Temik®, if appropriately reasoned and presented. The data of Pizarro et al. represent a controlled study in a human population in which a carefully measured dose was used to measure a subtle adverse response. The Poirier et al. data, even in abstract form, could also be used to corroborate the Pizarro et al. data with an additional population size of 179 male and female subjects.

There are also some general methodological issues in this document, that although we were not requested to comment upon I feel compelled to mention nonetheless. The document routinely performs route-to-route extrapolations of inhalation RfC values to a value termed RfD_{inhal} to convert mg^3/m to a mg/kg·day value. There is no toxicological basis provided for performing these conversions and the results have no toxicological justification or significance. Furthermore, the default values used in these calculations are from exposure assessment documents and are not consistent with typical toxicological values used in these types of calculations when performed under justifiable circumstances. No consideration is given to whether or not portal-of-entry effects, *i.e.* effects that are observed only in the lung, are present which would preclude conversion of inhalation RfC values to units of dose. Calculations such as the AEL_{inhal} for copper incorrectly utilize temporal correction methods, *i.e.* normalization of occupational exposure times to average chronic exposure periods, and selection of uncertainty factors are inconsistent with the published EPA guidelines. I did not look at the values for the other trace elements found at the site, but I would be hesitant to use these values for any type of remediation decision until they have been reviewed in sufficient detail.

Is speciation of the copper in Hurley soil appropriate? Speciation of copper is appropriate. In the studies that we are have conducted, as well as those of Pizarro et al., the copper salt chosen was the sulfate, one of the more soluble copper salts and assumed to be one of the more bioavailable salts as well. Most water supplies contain oxides or carbonate salts of copper that are not very readily bioavailable. Thus, studies performed with the sulfate salts are more conservative in the sense that exposure represents a worse case scenario. Likewise, when looking at remediation site, knowledge of the type of copper present is appropriate, as it will provide the risk manager a sense of relative bioavailability. Copper sulfate is considerably more bioavailable than copper as other salts or copper in complex. A relative measure of solubility in a system approximating stomach conditions would be useful in getting a better understanding as to how these different copper species may react in a mammalian system.

Has the presence of other toxic metals in Hurley soils adequately been considered for their potential cumulative and synergistic effects? This topic was treated briefly in the HHRA. However, given the general state of knowledge on the risk assessment of chemical mixtures and specifically that of copper, there is very little that can be estimated from the data without considerable inference and departure from standard scientific methods.

Is it reasonable to consider episodes of high soil ingestion? This is more of an exposure assessment and risk management question rather than that of a toxicological risk assessment issue. However, let me wage in with a personal opinion. The acute effects of GI disturbance occur in a very specific exposure situation – copper in drinking water causing direct portal-of-entry effects (in this case the effects of copper occur directly on the gastrointestinal tract, *i.e.*

stomach) that are of a rapid onset and quite transient in nature. It should be noted that individuals who consume multivitamins ingest copper in a large dose similar to that received in drinking water, but these individuals do not appear to develop symptoms of GI disturbance. At least as yet these symptoms have not been reported in the literature. Copper in nutritional supplements is given in forms most likely to be bioavailable to the user. Individuals ingesting soil would be subject to a dose of copper that is in an unknown form, but likely to be less bioavailable than copper in multivitamins. Although GI effects are possible in this scenario, I would expect acute effects of copper from soil pica to be unlikely. However, a more thorough analysis of this exposure route would be recommended before a definitive statement could be made.

Is copper essentiality necessary to consider when attempting to establish a soil cleanup level?
Although a working paradigm has not been established by any regulatory agency, it is imperative to balance the risk assessment of essential elements in site remediation especially when worst case scenarios, *i.e.* default assumptions and models, are used to drive the risk and exposure assessments. While soil is not a normal route of copper intake, a lack of regard for the essentiality of copper will result in an overly conservative and perhaps unnecessary site remediation. Unfortunately, this is a general opinion and does not offer specifics. The best advice I could give is to balance the essentiality and toxicity of the essential element through a weight of evidence analysis. A part of this weight of evidence analysis should include what is known about the essentiality of copper for which there is clearly more information available than for the toxicity of this trace element. Remediation without considering copper essentiality, possible exposure routes, form or salt of copper or an appropriate RfD calculation would not appropriately address this weight of evidence consideration.

I hope this information is useful to you. I expect that this response may raise additional questions. Please feel free to contact me for clarification.

Sincerely,

Kenneth A. Poirier

Kenneth A. Poirier, Ph.D.
Research Program Manager

Cc: Joan Dollarhide